Hematology Recommendations and Dosing Guidelines during COVID-19

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Note: Research on COVID 19 is emerging rapidly. As such, this document is fluid and will be updated regularly. An important thread in all of these recommendations is to take an individualized approach to patient management and a call for prospective randomized clinical trials to address important anticoagulation issues in this population.

I. Recommendations
   a. Diagnostics: For all patients presenting to MGH for COVID-19:
      i. Obtain baseline: D-dimer, PT, PTT, fibrinogen, ferritin, LDH, troponin, CPK, CK and CBC with differential
   b. Monitoring
      i. Trend D-dimer daily (or whenever labs are being drawn if less frequent) if baseline or subsequent >1000 ng/mL. (A,B,D,E) [1-6]
      ii. For patients in the ICU, trend CBC, PT, PTT and fibrinogen daily (or whenever labs are being drawn if less frequent) (D,E) [6-11]
   c. Management
      i. All patients admitted to MGH for COVID-19 (including non-critically ill) should receive standard prophylactic anticoagulation with LMWH (see Dosing Guidelines, [12]) in the absence of any contraindications (active bleeding or platelet count less than 25,000); monitoring advised in severe renal impairment; abnormal PT or APTT is not a contraindication (C) [13-18]  
         1. If CrCl >30mL/min – use Lovenox 40mg sc daily
         2. If CrCl <30mL/min – use UFH (see Dosing Guidelines).
3. In obese patients (BMI >40 kg/m² or >120 kg), the recommended dose is 40 mg bid (for renal failure, see Dosing Guidelines)
4. If history of HIT or HITT, use non heparin alternative.
5. If anticoagulation is contraindicated, patients should have mechanical prophylaxis (eg: pneumoboots).

ii. Patients admitted to MGH who are on a direct oral anticoagulant or warfarin as an outpatient (eg. for atrial fibrillation, h/o VTE, prosthetic valves) should be switched to therapeutic dose of LMWH (preferred over UFH to decrease blood draws to monitor PTT) due to possible interactions with COVID 19 treatments. [9]

iii. If patient has a confirmed acute DVT or PE or was on therapeutic anticoagulation prior to hospitalization and now changed to parenteral, the following guidelines are recommended:
   1. LMWH is preferred, to minimize blood draws and has superior efficancy in critical care population [19-20]. (See Dosing Guidelines for special populations and alternatives for renal failure)
   2. Patients who need to be on Unfractionated Heparin (instead of LMWH) should be monitored with antiXa levels (as opposed to PTT given that the latter increases in severely ill COVID-19 patients and may render the PTT unreliable).

iv. Page the inpatient Hematology Consult attending at any time to discuss specific guidance if a patient’s coagulopathy appears to be worsening or to discuss enhanced or changed treatment approach.

v. Whether or not COVID-19 infected patients have a unique increased risk of VTE compared to other critical infections/processes is not currently known, and is an area of active research. [3-6, 21-27] At this time, we do not suggest escalating prophylactic dose of anticoagulation. Several randomized controlled trial are currently addressing this question, and we encourage participation for eligible patients. At MGH, the trial, A Randomized, Open-Label Trial of Therapeutic Anticoagulation in COVID-19 Patients with an Elevated D-Dimer, is open and enrolling.

vi. We suggest limiting therapeutic anticoagulation to the following COVID-19 patients:
   1. Documented acute DVT/PE (see next section)
   2. Pre-hospitalization management with therapeutic anticoagulation (as for Afib, certain mechanical heart valves, recurrent VTE, etc)

Note: Please contact renal for CVVH related clotting protocol
vii. Currently, there is insufficient data to suggest using more advanced therapies (such as TPA) in critically ill COVID-19 patients without other indication, and we do not recommend it at this time. Trials are underway investigating these agents.

viii. Currently, the risk-benefit ratio of postdischarge thromboprophylaxis remains uncertain and there is insufficient data to recommend routine venous thromboprophylaxis post-discharge in patients with COVID without a clear indication (eg. major surgery). (F) [28-30] Trial addressing this issue are underway.

d. Evaluation for suspected VTE
i. Concern for DVT: Obtain venous Doppler study, if possible, to evaluate asymmetric limb pain or edema. If DVT is present, start full dose anticoagulation (LMWH preferred, see Dosing Guidelines). If patient is unable to get US due to concern of staff exposure to COVID-19, and clinical suspicion for DVT is high, we would suggest treating with full dose anticoagulation (unless contraindicated) (see Dosing Guidelines). Feel free to page the inpatient Hematology Consult attending for any guidance.

ii. Concern for PE: This is a challenge given the inherent hypoxia and perturbed coagulation profile of COVID-19 infected patients.
   1. Consider PE in the case of:
      a. Marked increase/rising Ddimer from priors AND
      b. Acute worsening of oxygenation, blood pressure, tachycardia with imaging findings NOT consistent with worsening COVID-19 PNA
   2. During the COVID pandemic, standard diagnostic evaluation (CTA, ECHO) may not be possible.
      a. if possible, obtain US and if + DVT, treat with full dose anticoagulation or
      b. if possible, obtain point of care ECHO and if evidence of acute, otherwise unexplained right heart strain and high clinical suspicious for PE, or intra-cardiac thrombus, treat with full dose anticoagulation.
      c. If patient unable to get US or ECHO due to concern of staff exposure to COVID-19 and clinical suspicion for PE remains high, we would suggest treating with full dose anticoagulation (unless contraindicated) (see Dosing Guidelines).
   3. Using a multidisciplinary approach, as offered by the Pulmonary Embolism Response Team (PERT), can greatly assist in these complicated patients. [31]

e. Bleeding concerns
i. Currently, there is limited data available regarding bleeding issues in the setting of COVID-19. (G) [3,26,32] If bleeding does develop, similar principles to septic
coagulopathy as per the ISTH guidelines with respect to blood transfusions may be followed. [6]

II. Heme Contact
Please contact the Hematology Consult Attending for any coagulation-related COVID-19 issues or questions.

Notes:

(A) D-dimer
- It is already well-established that older individuals and those who have co-morbidities (both groups tend to have higher D-dimer) are more likely to die from COVID-19 infection. [1]
- Studies specifically looking at abnormal coagulation parameters have identified markedly elevated D-dimers as one of the predictors of mortality. [2,3,4,5,6]
- Al-Samkari and colleagues demonstrated that elevated D-dimer at initial presentation was predictive of coagulation-associated complications during hospitalization (D-dimer >2500 ng/mL, adjusted odds ratio [OR] for thrombosis, 6.79 [95% CI, 2.39-19.30]; adjusted OR for bleeding, 3.56 [95% CI, 1.01-12.66]), critical illness, and death. [3]
- Huang and colleagues showed that D-dimer levels on admission were higher in patients needing critical care support (median [range] D-dimer level 2400 ng/mL [600–14,400]) than those patients who did not require it (median [range] D-dimer level 0·5 ng/nL [300–800], p=0-0042). [4]
- Zhou and colleagues showed that elevated D-dimer levels (>1g/L) were strongly associated with in-hospital death (OR 18.4 95% CI 2.6-128.6, p=0.003) [5]

Comments regarding D-dimer: When thrombin is activated, it cleaves fibrinogen into fibrin. The fibrin then polymerizes and is cross-linked by Factor XIII. When such a fibrin clot is generated in any disorder, microvascular or macrovascular, the fibrinolytic system is activated, and plasmin cleaves the cross-linked fibrin into smaller pieces which are the D-dimers. Therefore, the D-dimer reflects the production of cross-linked fibrin and is also affected by hepatic function; D-dimers are cleared by a normal liver but rise with liver dysfunction.

(B) DIC
- Tang et al noted development of DIC on day 4 in 71.4% of patients who didn’t survive the infection compared to just 1 patient (0.6%) who survived. Researchers also noted a statistically significant increase in D-dimer levels, and PT with a decrease in fibrinogen levels in non-survivors at days 10 and 14. [2,6]

(C) LMWH
- LMWH protects critically ill patients against venous thromboembolism. In addition, LMWH has been shown to have anti-inflammatory properties which may be an added benefit in COVID infection where proinflammatory cytokines are markedly raised. [1,4,9,18,19]. See dosing instructions below. [12]

(D) Monitoring
- Multi-organ failure is more likely in patients with sepsis if they develop coagulopathy and inhibiting thrombin generation may have benefit in reducing mortality. [7,8,9]. As noted in (B), this evidence suggests that monitoring PT, D-dimer, platelet count and fibrinogen can be helpful in determining prognosis in COVID-19 patients and if there is worsening of these parameters, more aggressive critical care support is warranted and consideration should be given for more ‘experimental’ therapies in and blood product support as appropriate [2,4,9]

(E) Thrombocytopenia
Subgroup analysis comparing patients by survival noted lower platelet count correlated with mortality. Thrombocytopenia was also associated with over five-fold increased risk of severe COVID-19 illness (OR, 5.1; 95% CI, 1.8-14.6). This suggests thrombocytopenia at presentation may be prognosticator. [11]

Al-Samkari and colleagues showed that thrombocytopenia (platelet count <150 × 10^9/L) and elevations in D-dimer >2500 ng/mL at initial presentation were predictive of bleeding complications during hospitalization (in multivariable analysis, for platelet count <150 × 10^9/L: OR, 2.90; 95% CI, 1.05-7.99; and for D-dimer >2500 ng/mL: OR, 3.56; 95% CI, 1.01-12.66). [3]

(F) Post-discharge prophylaxis

- The rates of thrombosis and hemorrhage appear to be similar following hospital discharge for COVID. Patell and colleagues showed that the cumulative incidence of VTE alone at day 30 postdischarge was 0.6% (95% CI, 0.1-4.6). The 30-day cumulative incidence of major hemorrhage was 0.7% (95% CI, 0.1-5.1) and of clinically relevant nonmajor bleeds was 2.9% (95% CI, 1.0-9.1). These findings emphasize the need for randomized data to inform recommendations for universal postdischarge thromboprophylaxis. [28]

- Roberts and colleagues demonstrated that COVID hospitalization does not appear to increase the risk of postdischarge hospital-associated VTE (HA-VTE) compared with hospitalization with other acute medical illness. Following 1877 hospital discharges associated with COVID, 9 episodes of HA-VTE were diagnosed within 42 days, giving a postdischarge rate of 4.8 per 1000 discharges. [29]

- Hill and colleagues reported that after a median follow-up of 14.6 days, VTE had been diagnosed in 3 of the 2075 admitted who were discharged alive (0.14%). Pending further evidence from prospective, controlled trials, their findings support a traditional approach to primary VTE prevention in patients with COVID-19. [30]

(G) Bleeding Complications

- In an autopsy study of 82 patients, Zhang and colleagues found that hemorrhage accounted for 6.1% of the deaths and hemorrhagic damage was found in 80.5% of patients. [21]

- Fraisse and colleagues reported on 92 patients with COVID and found a 21% rate of significant hemorrhagic events, with most of them occurring in patients with full-dose anticoagulation; however, half of the patients were treated with full-dose preemptive anticoagulation without a confirmed TE. [22]
**Dosing Guidelines (see attached charts) [12]**

### Suppemental Table S1: Chemoprophylaxis Dosing Recommendations

<table>
<thead>
<tr>
<th>Natural Route</th>
<th>Enoxaparin&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Fondaparinux&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Dabigatran&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Dose</strong></td>
<td>5000 units SQ q12h</td>
<td>40 mg SQ q24h</td>
<td>2.5 mg PO q12h</td>
<td>10 mg PO q24h</td>
<td>110 mg x 1 on post-op day 9 followed by 220 mg q24h</td>
</tr>
<tr>
<td><strong>Renal Adjustment</strong></td>
<td>No dose adjustment required</td>
<td>CrCl 15 - 29 mL/min: 30 mg SQ q24h</td>
<td>CrCl &lt; 15 mL/min or on renal replacement therapy: Consult Pharmacy</td>
<td>Avoid use if CrCl &lt; 15 mL/min</td>
<td>Avoid use if CrCl &lt; 15 mL/min</td>
</tr>
<tr>
<td><strong>Obesity</strong> (BMI &gt; 40 kg/m², weight &gt; 120 kg)</td>
<td>120 - 150 kg: 5000 units q8h &gt; 150 kg: 7500 units q8h</td>
<td>CrCl &gt; 30 mL/min: 40 mg SQ q12h</td>
<td>CrCl &lt; 30 mL/min or on renal replacement therapy: Consult Pharmacy</td>
<td>Limited Data, Consult Pharmacy</td>
<td>Limited Data, Avoid Use</td>
</tr>
<tr>
<td><strong>Low Body Weight (&lt; 50 kg)</strong></td>
<td>5000 units SQ q12h or 2500 units SQ q12h</td>
<td>30 mg SQ q24h</td>
<td>Limited Data, Avoid Use</td>
<td>Limited Data, Avoid Use</td>
<td>Limited Data, Avoid Use</td>
</tr>
<tr>
<td><strong>Drug-Drug Interactions</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Major DDI Consult Pharmacy</td>
<td>Major DDI Consult Pharmacy</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Consult pharmacy or hematology in patients with organ dysfunction, extremes of weight or close monitoring warranted (e.g., high blood risk, failure to thrive); consider drug-specific anti-Xa monitoring</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AKI – acute kidney injury; BMI – body mass index; DDI – drug drug interactions; PO – per os (oral route); SQ – subcutaneous route

### Suppemental Table S2: Therapeutic Parenteral Anticoagulation Recommendations

<table>
<thead>
<tr>
<th>Unfractionated Heparin</th>
<th>Enoxaparin&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Fondaparinux&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Bivalirudin&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Dose</strong></td>
<td>ACS: 60 unit/kg bolus + 12 units/kg hr infusion VTE/Afib: 80 unit/kg bolus + 18 units/kg hr infusion</td>
<td>1 mg/kg SQ q12h (for normal renal function)</td>
<td>Weight-based: &lt; 50 kg: 5 mg SQ q24h 50 - 100 kg: 7.5 mg SQ q24h &gt; 100 kg: 10 mg SQ q24h</td>
<td>See Protocol – Standard Starting Dose: 0.15 mg/kg/hr</td>
</tr>
<tr>
<td><strong>Renal Adjustment</strong></td>
<td>CrCl 15 – 29 mL/min: 1 mg/kg SQ q4h CrCl &lt; 15 mL/min: Consult Pharmacy</td>
<td>CrCl &lt; 30 mL/min: Avoid use</td>
<td>CrCl 30 – 60 mL/min: 0.05 mg/kg/hr CrCl &lt; 30 mL/min or on Renal Replacement Therapy: 0.025 mg/kg/hr</td>
<td>No Dose Adjustment Necessary</td>
</tr>
<tr>
<td><strong>Hepatic Adjustment</strong></td>
<td>No Dose Adjustment Necessary</td>
<td>No Dose Adjustment Necessary</td>
<td>No Dose Adjustment Necessary</td>
<td>No Dose Adjustment Necessary</td>
</tr>
<tr>
<td><strong>Obesity</strong> (BMI &gt; 40 kg/m², weight &gt;120 kg)</td>
<td>Consult Pharmacy</td>
<td>CrCl &gt;30 mL/min: 0.75 mg/kg q12h CrCl &lt; 30 mL/min: 0.75 mg/kg q24h &gt; 150 kg: Avoid Use</td>
<td>&gt; 100 kg: 10 mg SQ q24h</td>
<td>Limited data, Consult Pharmacy</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACS – acute coronary syndrome; Afib – atrial fibrillation; BMI – body mass index; SQ – subcutaneous route; VTE – veno-venous thrombosis
References


